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Organelles in focus

Calcium-activated potassium channels: implications for aging and age-related neurodegeneration

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ABSTRACT

Population aging, as well as the handling of age-associated diseases, is a worldwide increasing concern. Among them, Alzheimer's disease stands out as the major cause of dementia culminating in full dependence on other people for basic functions. However, despite numerous efforts, in the last decades, there was no new approved therapeutic drug for the treatment of the disease. Calcium-activated potassium channels have emerged as a potential tool for neuronal protection by modulating intracellular calcium signaling. Their subcellular localization is determinant of their functional effects. When located on the plasma membrane of neuronal cells, they can modulate synaptic function, while their activation at the inner mitochondrial membrane has a neuroprotective potential via the attenuation of mitochondrial reactive oxygen species in conditions of oxidative stress. Here we review the dual role of these channels in the aging phenotype and Alzheimer's disease pathology and discuss their potential use as a therapeutic tool.

1. Introduction

Life expectancy has increased by 10 years in the last 60 years (Eatock 2019) and population aging, as well as the handling of age-associated diseases, is a worldwide increasing concern. According to the World Health Organization, the world's population over 60 will nearly double by 2050, which translates into more than 2 billion people (Chatterji 2013) and directly affects the course of health and economic policies. Among age-related pathologies, currently, more than 1 billion people are affected by neurodegenerative diseases, and almost 7 million deaths annually result from these conditions (Group, GBD, 2015, Erkinen et al., 2018). Among them, Alzheimer's disease (AD) is considered to be the current major cause of dementia and ultimately leads to full dependence on relatives or nursing care for basic functions (Erkinen et al., 2018).

Different therapeutic strategies have been explored over the years in an attempt to alleviate the symptoms or slow down the progression of the disease (Godýn et al. 2016). United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved drugs for AD are the N-methyl-D-aspartate receptor (NMDA) antagonist memantine, which acts mainly by reducing glutamate excitatory activity; and acetylcholinesterase inhibitors, tacrine, donepezil,

galantamine, and rivastigmine, which increase the active-life of the neurotransmitter acetylcholine (Colović et al. 2013, Matsunaga et al., 2015). Nonetheless, since memantine approval in the early 2000s, there was no new approved therapeutic drug for AD despite numerous efforts, highlighting the importance of exploring new targets for preventing neurodegeneration. Importantly, these drugs are not curing AD patients (Fig. 1).

In the past decade, calcium-activated potassium channels (K_{Ca}) have emerged as a potential tool for neuronal protection (Malinska et al., 2010, Su et al. 2017, Sugunan et al. 2016, Piwońska et al. 2016, Dolga et al. 2011, Dolga and Culmsee 2012, Dolga et al. 2012, Herrik et al. 2012). Among the different K^+ selective channels and transporters, calcium-activated potassium channels stand out for directly linking K^+ dynamics to Ca^{2+} signaling.

In this review, we discuss the alterations in K_{Ca} channel activity and the influence of its subcellular localization during aging and neurodegenerative disease onset. Subsequently, we address the prospective therapeutic use of their modulators exploring potential benefits and pitfalls.

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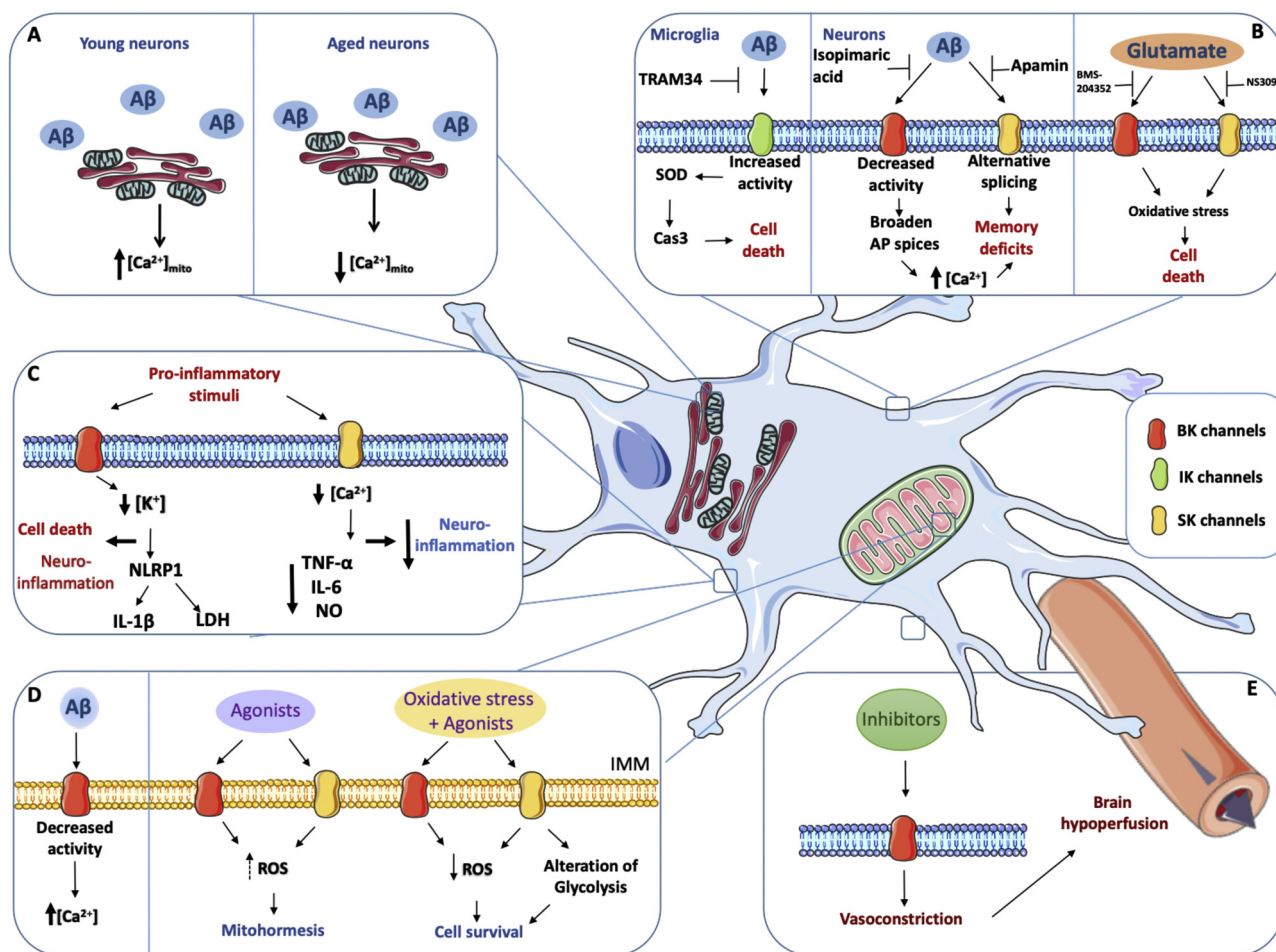


Fig. 1. Involvement of KCa channels in neurodegenerative conditions.

Presented in the figure are several mechanisms where KCa channels in organelles or on the plasma membrane (PM) play a role in neurodegeneration and neuroinflammation, including some effects that Amyloid-beta ($A\beta$) has on their open probability. $A\beta$ oligomer treatment in aged neurons led to decreased mitochondrial calcium (Ca^{2+}) concentration (A). $A\beta$ has differential effects on KCa opening on the PM. While the $A\beta$ increases the open probability of IKCa and SKCa channels, leading respectively to cas3 dependent cell death or memory deficits, the open probability of BKCa channel is decreased, resulting in enhanced cytosolic Ca^{2+} and ER stress (B). Also on the PM, pro-inflammatory stimuli, being a risk factor for neurodegenerative diseases, affect KCa channels (C). Here, increased BKCa channel currents and consequently, K^+ efflux activates the NLRP1 inflammasome pathway leading to neuroinflammation, increased expression of lactate dehydrogenase (LDH) and IL-1 β , and neuronal apoptotic rates. On the other hand, SKCa channel activation in conditions of LPS-induced inflammation in microglia lead to attenuated neuroinflammation via decreasing intracellular Ca^{2+} levels and reducing downstream events including TNF- α and IL-6 cytokine production and nitric oxide (NO) release (C). At the IMM activation of both SKCa and BKCa channels induces mitohormetic effects that restore the oxidative balance and lead to cell survival. The effects that $A\beta$ deposition has on the KCa channels in the mitochondria include decreased BKCa channel activity and enhanced Ca^{2+} levels in the mitochondria (D). BKCa channels at the perivascular endfeet of astrocytes modulate vasodilatation and contraction in response to neuronal activation; their inhibition attenuates vasodilatation and contributes to brain hypoperfusion (E). Figure designed using Servier Medical Art.

2. KCa channels and Ca^{2+} homeostasis

The KCa family of proteins can be further divided into large ($KCa_{1.1}$ /BK Ca /BK), intermediate ($KCa_{3.1}$ /SK4/IK Ca /IK), and small ($KCa_{2.1-2.3}$ /SK Ca /SK) conductance channels. KCa channels are usually found in complexes with voltage-gated Ca^{2+} channels (Grunnet and Kaufmann 2004). Changes in intracellular Ca^{2+} concentration increase the open probability of KCa channels (Fakler and Adelman 2008), and in turn, membrane hyperpolarization resulting from K^+ efflux can deactivate voltage-gated Ca^{2+} channels, limiting Ca^{2+} entry (Brenner et al. 2000).

2.1. BK/ $KCa_{1.1}$ channels

Large conductance calcium-activated potassium (BK) channels display a conductance of 100-300 pS. BK Ca channels are composed of two distinct subunits, α and β , and are arranged as tetramers of α -subunits, each associated, or not, to a β -subunit at its N-terminal portion (1:1). The α -subunits have seven transmembrane domains (S0-S6), a pore-

forming loop (P-loop) between S5 and S6, and hydrophobic portions (S7-S10) at the C-terminus (Butler et al. 1993). The four α -subunits combine to form the K^+ selective pore and acid aminoacid residues in S2 and S3, as well as basic residues in S4, permit conformational changes depending on the charge of those residues that translates into voltage sensitivity to the channel. They are activated by voltage and Ca^{2+} modulates their open probability. The α -subunit C-terminal portion contains several regulatory sites, including the " Ca^{2+} bowl" motif at S10, which are the main responsible for Ca^{2+} sensibility. The β -subunits activity increases the channels Ca^{2+} sensibility (Wei et al. 1994, Ghatta et al. 2006, Brenner et al. 2000).

BK Ca channels display a lower affinity for Ca^{2+} when compared to the other subgroups of the family, having a half-maximal effective concentration (EC_{50}) of approximately 10 μ M at 30 mV compared to EC_{50} of 0.3 and 0.5 μ M of IK Ca and SK Ca channels, respectively (Zhang et al. 2018). Therefore, their activation takes place either when these channels are coupled to Ca^{2+} influx sources, such as NMDA receptor-mediated Ca^{2+} channels and L-type CaV, or when global intracellular

Ca^{2+} concentration is above the physiological concentration, which is about 0.1 μM in rest and 1 μM in an excitatory state (Zhang et al. 2018, Berkefeld and Fakler 2008). The kinetic of this activation is strongly influenced by the β subunit isoform (Sarga et al. 2013).

BK_{Ca} channels are extensively expressed in the central nervous system (CNS), being found in neurons, microglia, astrocytes and also in myocytes (Tseng-Crank et al. 1994, Contet et al. 2016, Longden et al. 2011). Presynaptically located BK_{Ca} channels' activity in CA3 pyramidal neurons leads to an inhibition of neurotransmitter release by hyperpolarizing the plasma membrane in response to depolarization and increased synaptic failure rate, preventing overexcitation. These channels' function is highly dependent on its intracellular localization, when located in dendrites their activity leads to repolarization of dendritic calcium spikes, regulating their duration and magnitude (Bock and Stuart 2016). In addition, the activity of mitochondrial located channels enhances cell viability by reducing ROS production and mitochondrial Ca^{2+} content (Balderas et al. 2015).

2.2. $\text{IK}/\text{K}_{\text{Ca}3.1}$ channels

Intermediate conductance calcium-activated potassium (IK_{Ca}) channels display a conductance of 25-100 pS and have a EC_{50} for Ca^{2+} of 0.3 μM (Zhang et al. 2018). Both IK_{Ca} and SK_{Ca} channels are structurally very similar to BK_{Ca} channels. Their α -subunit S4 transmembrane domain presents a lower number of acidic residues compared to BK_{Ca} channels, rendering it insensitive to voltage. IK_{Ca} and SK_{Ca} channels possess six transmembrane domains (S1–S6) and a conducting pore located between S5 and S6 (Köhler et al. 1996, Joiner et al. 1997, Logsdon et al. 1997, Ishii et al. 1997). IK_{Ca} and SK_{Ca} channels also lack the S0 transmembrane domain, and their higher Ca^{2+} sensitivity is mediated by the constitutive association of the Ca^{2+} -binding protein calmodulin (CAM) to the α -subunit C-terminal portion through the calmodulin-binding domain. In both IK_{Ca} and SK_{Ca} channels, binding of Ca^{2+} to CAM results in conformational changes that are responsible for channel gating and subsequent channel opening and K^{+} efflux. In addition, these conformational changes enable the channels to open during membrane hyperpolarization in excitable cells, which is less likely for BK_{Ca} channels (Catacuzzeno et al., 2012, Maylie et al. 2004, Lee and MacKinnon 2018, Coetzee et al. 1999). The IK_{Ca} channel is normally activated by global Ca^{2+} signals resulting from Ca^{2+} released from intracellular stores, or by influx through store operated Ca^{2+} channels (SOCs) present in the endoplasmic reticulum (ER). Moreover, in excitable cells, IK_{Ca} channel activation-induced cell hyperpolarization actually increases the driving force for Ca^{2+} entry through SOCs. This massive Ca^{2+} influx namely activates Ca^{2+} -dependent ion channels, and efflux of K^{+} ions following Ca^{2+} influx hyperpolarizes the membrane and increases the driving force for Ca^{2+} (Millership et al. 2011, Mark Duffy et al. 2004, Shepherd et al. 2007).

IK_{Ca} channels are expressed by enteric, sensory and sympathetic neurons, being associated with a slow afterhyperpolarization, between 5 and 30 s, against the average of 100-500 ms (Neylon et al. 2004, Sah 1996). Contrasting with the intracellular localization of BK_{Ca} channels, IK_{Ca} channel expression is not found in presynaptic regions. Instead, within the CNS, IK_{Ca} channels are expressed in the somatic region of cortical excitatory neurons, and somatic regions and dendritic segments of inhibitory neurons in the hippocampus and cerebellar Purkinje neurons (Turner et al. 2015). Nonetheless, these channels are mainly found in brain tumors, astrocytes, microglia (Blomster et al. 2016), and endothelial cells. As it is observed with BK_{Ca} channels, IK_{Ca} channels are expressed in astrocytes endfeet, playing an essential role in neurovascular coupling (Longden et al. 2011).

2.2.1. SK channels ($\text{K}_{\text{Ca}2.1}/\text{K}_{\text{Ca}2.2}/\text{K}_{\text{Ca}2.3}$)

Small conductance calcium-activated potassium (SK_{Ca}) channels display a conductance of 2-25 pS with an EC_{50} for Ca^{2+} of 0.5 μM . They are in structure very similar to IK_{Ca} channels. SK_{Ca} channels are mainly

expressed in the central and peripheral nervous system. Its three members, $\text{K}_{\text{Ca}2.1}/\text{SK1}$, $\text{K}_{\text{Ca}2.2}/\text{SK2}$, and $\text{K}_{\text{Ca}2.3}/\text{SK3}$ are differentially expressed in the human brain (Willis et al. 2017). When located in somatic regions, SK_{Ca} channels facilitate NMDA receptor (NMDAR) Mg^{2+} blockade, limiting Ca^{2+} influx and determining afterhyperpolarization and intrinsic excitability (Pedarzani and Stocker 2008, Bloodgood and Sabatini 2007, Chen et al., 2014, Allen et al. 2011), and therefore suggesting that targeting SK_{Ca} channels might have therapeutic value by modulating their effects on Ca^{2+} signaling and NMDAR. On the other hand, when located in pyramidal neurons dendritic spines, SK_{Ca} channels influence the amplitude of excitatory postsynaptic potentials by limiting local Ca^{2+} influx and increasing the threshold for long term potentiation (LTP) and synaptic plasticity (Jones and Stuart 2013). Thus, as observed with the other K_{Ca} channels, their subcellular localization is deeply related to their function and might affect their potentiality as therapeutic targets (Kuiper et al. 2012, Krabbendam et al. 2018). K_{Ca} channels are also found to be expressed in mitochondrial and ER membranes and to play a role in ER- Ca^{2+} intake (Kuum et al. 2012, Krabbendam et al. 2018). In addition, K_{Ca} channels expressed in the inner mitochondrial membrane, which are responsible for the transport of K^{+} from the highly concentrated cytosol to the mitochondrial matrix, lead to depolarization of the mitochondrial membrane and reduced Ca^{2+} intake, affecting ATP production, viability, metabolism and ROS generation (Laskowski et al. 2016).

In summary, it is important to keep in mind that K_{Ca} channels' different voltage and Ca^{2+} sensitivity properties lead to different intracellular $[\text{Ca}^{2+}]$ signaling resulting in different cellular phenotypes.

3. The aging CNS in health and disease

The aging process is characterized by a cascade of cellular alterations that culminates in the organism's functional decline. Its hallmarks have been extensively studied in the last decades and include features such as genomic instability, telomere shortening, altered epigenetic patterns, proteostasis loss, deregulated nutrient-sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín et al. 2013). The tissue microenvironment equally undergoes deep changes, and aging has been associated with altered secretome, modifications in the extracellular matrix composition, and increased background inflammation (Ueno et al. 2018, Lin et al. 2018). In fact, inflammaging, the chronic low-grade inflammation characteristic of aging, and immunosenescence, which leads to an impaired immune response to new antigens, play a major role in the development of age-related diseases. As observed in other tissues, in the central nervous system (CNS), the aging process correlates to a significant increase in basal levels of pro-inflammatory factors such as $\text{TNF-}\alpha$ (Tumor necrosis factor α) and the cytokines IL-6 (Interleukin-6) and IL-8 (Interleukin-8) (Bodles and Barger 2004, Ye and Johnson 1999, 2001, Hu et al. 2019). Moreover, an increase in senescent microglia is observed, leading to a slower, although more lasting, response to stimuli, - what can be explained by senescent-induced morphologic dystrophy; which includes features such as hypertrophic cytoplasm, fragmented processes, impaired phagocytosis, and reduced process motility and migration (Damani et al. 2011, Streit et al. 2004). This pro-inflammatory environment is accompanied by increased oxidative stress and is partly due to the senescence-associated secretory phenotype of activated astrocytes and microglia (Chinta et al. 2015).

Mitochondria, organelles responsible for oxidative phosphorylation, go through significant alterations with aging (López-Otín et al. 2013), displaying altered fission and fusion dynamics; decreased glucose metabolism and membrane depolarization; impairment in oxidative phosphorylation, Ca^{2+} signaling, and anti-oxidative mechanisms; as well as increased reactive oxygen species (ROS) production (Bereiter-Hahn 2014). The CNS is particularly affected since its main source of ATP is through oxidative phosphorylation, consuming around 20% of the organism's total inhaled O_2 in a rest state (Kann and Kovács 2007).

Aged neurons display higher Ca^{2+} cytosolic levels partially due to an enhanced Ca^{2+} influx through voltage-dependent Ca^{2+} channels. An increased Ca^{2+} transfer from the ER to mitochondria through mitochondria-ER membrane contact points is also observed (Calvo-Rodríguez et al. 2016, Gant et al. 2015).

Intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) also affects synaptic activity and is determinant for depolarization and, therefore, for neuronal activity (Castelli et al. 2019). Imbalanced neuronal excitability is observed with aging in hippocampal neurons, which affects memory. $[\text{Ca}^{2+}]_i$ is decreased in CA1 pyramidal neurons, due to an augmented post burst afterhyperpolarization (Murphy et al. 2004, Oh et al., 2010), and increased in CA3 pyramidal neurons (Oh et al., 2016). It is well known that aging is the major risk factor for neurodegenerative diseases, with the above-mentioned aging hallmarks being associated with higher susceptibility to the development of these conditions (Hou et al. 2019). Among them, AD is the most prevalent, with its clinical onset accompanied by reactive microgliosis, dystrophic neurites, and loss of neurons and synapses (Mayeux and Stern 2012).

AD pathophysiology is characterized by the presence of hyperphosphorylated Tau and Amyloid β (A β) aggregates. Tau is a microtubule associated-protein mainly present in the axons of CNS neurons, therefore its hyperphosphorylated aggregates, neurofibrillary tangles (NFTs), impair axonal transport and neuron intercommunication (Congdon and Sigurdsson 2018). A β aggregates are found in the form of soluble oligomers and fibrils (A β -derived diffusible ligands) – which interact with different cell surface receptors and impair synaptic signaling. A β aggregates also form insoluble amyloid plaques, whose presence in the brain parenchyma and capillary vessel vicinities leads to an overall higher inflammatory status (Murphy and LeVine 2010, Qi and Ma 2017). Moreover, A β oligomers treatment is known to lead to long term potentiation inhibition and therefore decreased excitability (Yun et al. 2006, Pchitskaya et al., 2018).

It is interesting to note that γ -secretase enzymatic complex components, such as presenilin-1 (PSEN1) and presenilin-2 (PSEN2), which process amyloid precursor protein (APP) into A β , are enriched in mitochondria-ER membrane contact points (Molledo et al., 2019, Area-Gomez et al. 2009). Mutations in PSEN1, prevalent in familial cases of AD, result in a dysregulation of Ca^{2+} dynamics, with an increase in cytosolic Ca^{2+} associated with a decrease in mitochondrial Ca^{2+} (Korkotian et al., 2019). In addition, ER Ca^{2+} is found to be elevated in both aging and AD neurons (Bezprozvanny and Mattson 2008). Interestingly, the treatment of both young and aged neurons with A β oligomers lead to an increase in mitochondria-ER membrane contact points. While in young neurons this increase translated into an augmented transfer of Ca^{2+} from the ER to the mitochondria, in aged neurons this transfer was found to be significantly diminished, resulting in a decreased mitochondrial potential, increased ROS and apoptosis (Calvo-Rodríguez et al. 2019) (Fig. 1A). Thus, unbalanced Ca^{2+} homeostasis contributes to neurodegenerations and synaptic loss observed in aging and neurodegenerative conditions, impairing long-term potentiation and favoring long-term depression (topic extensively revised in (Bezprozvanny and Mattson 2008; Pchitskaya et al., 2018; Egorova et al., 2015)).

4. The role of K_{Ca} channels in CNS aging and AD pathophysiology

4.1. $\text{BK}/\text{K}_{\text{Ca}1.1}$ channels

BK_{Ca} channels voltage-sensitiveness and lower affinity for Ca^{2+} associated to its subcellular localization, determine their action either in the repolarization or the afterhyperpolarization phase of the neuronal action potential and can be either excitatory or inhibitory for neuronal firing activity. Thus, this dual role in the CNS deeply interferes with their therapeutic potential.

4.1.1. Alzheimer's Disease

Several studies on genome-wide association showed a potential relation between AD pathology (age-at-onset or disease duration) and a SNP in the gene encoding $\text{BK}_{\text{Ca}} \alpha$ (*KCNMA1*, rs16934131). In addition, hippocampal sclerosis, a comorbid neuropathological feature of AD was also shown to be associated with a SNP in the gene encoding $\text{BK}_{\text{Ca}} \beta 2$ (*KCNMB2*, rs9637454) (Beecham et al. 2009, Beecham et al. 2014, Burns et al. 2011). BK_{Ca} channel activity is deeply impaired by A β aggregates. Studies in rodent neurons showed that A β reduced BK_{Ca} current both at the plasma membrane and also in the mitochondrial fraction (Jafari et al. 2015). Neocortical pyramidal neurons intracellularly injected with A β (1-42) display a decreased BK_{Ca} channel activity, increasing Ca^{2+} influx and broader action potential spikes, a phenotype that is also observed in the 3xTg AD mice (Yamamoto et al. 2011, Wang et al. 2015) (Fig. 1B). Moreover, the infusion of isopimaric acid, a BK_{Ca} channel activator, into the ventricular-subarachnoid system reversed the action potential spike width and led to a better performance in the novel recognition test and Morris water maze (Wang et al. 2015). In agreement with these data, BK_{Ca} channel α -subunit knock-out mice displayed impaired spatial learning (Typl et al. 2013). Moreover, *Fmr1* knock out mice, a model for fragile X syndrome, when treated with BK_{Ca} channel activator BMS-204352, displayed a normalization of their dendritic spike pattern and glutamate homeostasis, in addition to their social recognition and interaction, non-social anxiety, and spatial memory (Hébert et al. 2014). BK_{Ca} and SK_{Ca} channel dysfunction is also associated with the spiking irregularity characteristic of spinocerebellar ataxia type 7 (SCA7). A low expression of BK_{Ca} channels, PGC-1 α acetylation, and impaired Sirt1 enzymatic activity are contributors to SCA7 pathology. In fact, BK_{Ca} channel overexpression into the deep cerebellar nucleus of SCA7 mice led to the restoration of spike regularity, highlighting the importance of BK_{Ca} channel neuronal expression for the mitochondrial function, neuronal network and neuromuscular interactions (Stoyas et al. 2020).

However, A β aggregates action is not limited to cellular membrane channels, intracerebroventricularly injected A β (1-42) induces a shift in BK_{Ca} channels composition in the inner mitochondrial membrane (IMM), with an increase in $\beta 4$ subunit and a concomitant decrease in α subunit expression. This variation in subunits composition leads to a decrease in BK_{Ca} channel activity and consequently in mitochondrial depolarizing potential (Jafari et al. 2015) (Fig. 1D).

Cerebrovascular abnormalities and hypoperfusion precede the clinical onset of AD and correlate to its progression (Binnewijzend et al. 2016, Ruitenberget al. 2005, Farkas and Luiten 2001). In this respect, astrocytes have a major role in the regulation of cerebral blood flow, functional hyperemia, and perivascular brain clearance (Attwell et al. 2010, Howarth 2014, Mawuenyega et al. 2010, Iliff et al. 2012, Benveniste et al. 2019, Tarantini et al. 2017). Neurovascular coupling dictates local vasodilatation and constriction in a process mediated by BK_{Ca} channels present in astrocyte endfeet (Girouard et al. 2010, Menyhart et al. 2018). Through this mechanism, small increases in $[\text{Ca}^{2+}]_i$ induce dilatation, however substantial increases induces constriction (Girouard et al. 2010). Therefore, an increased of $[\text{Ca}^{2+}]_i$ observed in AD could favor vasoconstriction while BK_{Ca} channel inhibition leads to an attenuation of the vasodilatation in response to neuronal activation (Girouard et al. 2010) (Fig. 1E). Moreover, of special interest is the glymphatic system, a mechanism dependent on AQ4 water channels present in astrocyte endfeet in which the cerebrospinal fluid in the periarterial vicinities is transported to the interstitial fluid (Benveniste et al. 2019, Iliff et al. 2012, Tarantini et al. 2017). AD cerebrovascular alterations affect the glymphatic system and have a major role in A β clearance deficiency and therefore in its accumulation in the CNS (Mawuenyega et al. 2010, Iliff et al. 2012). Interestingly, brain samples from AD patients and transgenic mice models for vascular A β deposition, displayed a substantial reduction in both AQ4 and astrocyte BK_{Ca} channels expression (Wilcock et al., 2009). Taken together, these reports indicate that BK_{Ca} channels dysfunction at

the perivascular astrocyte endfeet might impair function hyperemia, compromising clearance, neuronal function and nutrient availability contributing to AD progression and dementia.

4.1.2. Neuroinflammation

BK_{Ca} channels behavior upon different inflammatory stimuli and models have been described. Neuroinflammation is a key feature in AD, ergo the functionality of the resident immune cells of the CNS, the microglia is deeply intertwined with the development of the disease since its early stages (Hemonnot et al. 2019). Data on the microglial BK_{Ca} current in juvenile and aged mouse brains showed no difference in the BK_{Ca} current between various brain regions, or between ramified and dystrophic microglial cells, suggesting that the activity of BK_{Ca} might not be essential during aging (Schilling and Eder 2015). However, under pathological conditions, mimicked by lipopolysaccharide (LPS) application led to the activation of BK_{Ca} channels through a toll-like receptor 4 (TLR4)-mediated mechanism (Yang et al. 2019, Yeh et al. 2019). Both pharmacological application of paxiline and siRNA-mediated impairment of BK_{Ca} channel activity significantly inhibits LPS-induced primary mouse microglial activation (Yang et al. 2019). Moreover, chronic glucocorticoid exposure, which can be a result of chronic stress and a risk factor for neurodegenerative diseases, modeled by dexamethasone treatment, increased BK_{Ca} channel currents and consequently K⁺ efflux. In turn, low intracellular [K⁺] activated the NLRP1 inflammasome pathway leading to neuroinflammation, with increased expression of lactate dehydrogenase (LDH) and IL-1 β , and neuronal apoptotic rates (Zhang et al. 2017). These effects were reverted by the BK_{Ca} channel inhibitor iberiotoxin, indicating that BK_{Ca} channels play an essential role in regulating inflammatory signaling (Zhang et al. 2017) (Fig. 1C).

4.1.3. Synaptic regulation

Aging is associated with a decrease in neuronal excitability and longer afterhyperpolarization phases (Power et al. 2002). BK_{Ca} channel subtypes were shown to be differentially expressed due to aging in rat dorsal root ganglion neurons affecting their action potential after-hyperpolarization electrophysiological profile (Yu et al. 2015, Sesti 2016). Nonetheless, these channels are prone to oxidation by ROS in specific methionine and cysteine residues, which enhances their functionality by increasing the period these channels stay in an open conformation in pyramidal neurons of the hippocampus. This increased activity is reversed by treatment with reducing agents such as dithiothreitol (DTT) (Gong et al. 2000). Also, in *Drosophila* larval neuromuscular junction, blockage of BK_{Ca} channel activity increased synaptic transmission tolerance to acute H₂O₂-induced oxidative stress (Bollinger et al., 2018). Besides, an antioxidant supplemented diet with N-acetylcysteine, α -lipoic acid and α -tocopherol lead to ameliorated memory impairment in mice linked to changes in synaptosomal [K⁺] (Thakurta et al. 2014). In agreement with this data, AD transgenic mice harboring human-APP mutations exhibited depressed synaptic transmission associated with increased presynaptic BK_{Ca} channel activity in the CA1 hippocampus (Ye et al. 2010).

4.1.4. Mitochondrial function

BK_{Ca} channel activity in the mitochondria is equally important for neuronal function. BK_{Ca} channel SLO-1 *Drosophila melanogaster* mutants display mitochondria ultrastructural and functional defects, leading to an increase in ROS generation which is associated with a reduced lifespan. In addition, human BK_{Ca} channels overexpression in these male mutants lead to an increased lifespan (Gururaja Rao et al. 2019). However, BK_{Ca} channel SLO-1 knockdown and pharmacological inhibition with paxiline in *Caenorhabditis elegans* increased lifespan. Interestingly, this beneficial effect on the longevity of paxiline was detectable only in old-treated worms, while the young-treated worms did not benefit from the treatment. The function of the motor neurons was improved in both paxiline-treated worms and SLO-1 mutants (Li et al.

2019). These studies indicate that BK_{Ca} channels play a role in longevity and more studies are necessary to elucidate the potential alterations in expression, splice variants and species-specific effects.

On the other hand, mitochondrial BK_{Ca} channels have been implicated in the modulation of mitochondrial ROS production leading to mitochondrial preconditioning or mitohormesis, a process where mild stressors upregulate mitochondrial stress responses and confer protection (Raupach et al. 2019). Mice treated with the BK_{Ca} channel activator NS1619 and with the cell-permeant SOD mimetic MnTBAP showed reduced NS1619-induced ischemic preconditioning in an ischemia and reperfusion model. Interestingly, in a potential feedback loop, activation of BK_{Ca} channels present in the IMM, through the treatment with the agonists CGS 7184 and NS 1619, induced a reduction in ROS production in a complex I-dependent mechanism. This effect was reversed by co-treatment with BK_{Ca} channel inhibitors iberiotoxin and charybdotoxin (Kulawiak et al. 2008) (Fig. 1D). Moreover, the NS1619-dependent anti-inflammatory and mucosal permeability-sparing effects were ROS-dependent (Dai et al. 2017).

These results highlight BK_{Ca} channel dual role, at the same time that its activity contributes to synaptic dysfunction, it is important for spike pattern regulation and also has a neuroprotective function by regulating mitochondrial stress, rendering its modulation in a clinical setting challenging.

4.2. IK/K_{Ca}3.1 channels

4.2.1. Alzheimer's Disease

IK_{Ca} channels were shown to be involved in A β oligomer-induced reactive astrogliosis via its ability to increase the driving force for Ca²⁺ influx, proposing it as a target of interest for AD treatment.

Treatment with TRAM-34, a K_{Ca}3.1-specific inhibitor (Wulff et al. 2000), or the use of K_{Ca}3.1 knockout astrocytes leads to an attenuation of TGF- β induced astrogliosis by processes involving reducing intracellular calcium ([Ca²⁺]_i) (Yu et al. 2014). Furthermore, blocking K_{Ca}3.1 activity decreased A β oligomer-induced Ca²⁺ influx in astrocytes, suggesting that the K_{Ca}3.1 channel plays an important role in A β oligomer-induced reactive astrogliosis. Moreover, K_{Ca}3.1 inhibition through TRAM-34 treatment in the SAMP8 AD mouse model diminished microglia activation which was accompanied by preserved memory performance. A similar protective phenotype was observed when K_{Ca}3.1 knockout mice were administered with A β (1-42) in the intrahippocampal region and compared to wild type control (Yi et al. 2016). Gene deletion or pharmacological blockade of K_{Ca}3.1 has been shown to protect against store-operated Ca²⁺ entry (SOCE)-induced Ca²⁺ overload and ER stress via the protein kinase B (AKT) signaling pathway in astrocytes. Moreover, glial activation and neuroinflammation were attenuated in the hippocampi of APP/PSEN1 AD mice with *KCNN4* gene deletion, leading to reversed memory deficits and neuronal loss as compared with APP/PSEN1 AD mice (Yu et al. 2018). Although no role of IK_{Ca} channels concerning oxidative stress in AD has been reported in the literature, they do play a role in aging vascular endothelium, since several studies suggested that oxidative stress impaired IK_{Ca} function in old animals (Kong et al., 2015b, Choi et al. 2016, Behringer et al. 2013).

4.2.2. Neuroinflammation

In microglial cells, the activity of K_{Ca}3.1 channels has been associated with an activated microglial phenotype. Its inhibition through TRAM-34 treatment was described to decrease nitric oxide synthase expression and consequently nitric oxide and peroxynitrite production, which in turn lead to neuroprotection by decreasing neurotoxicity mediated by caspase 3 activation (Kaushal et al. 2007, Nguyen et al. 2017, Maezawa et al. 2011). Indeed, A β oligomer treatment increases K_{Ca}3.1 channel activity and A β oligomer-induced microglial neurotoxicity was prevented by TRAM-34 treatment (Maezawa et al. 2011, Jin et al. 2019) (Fig. 1B). In accordance with the mechanisms described,

K_{Ca}3.1 expression was increased in neurons and reactive astrocytes of brain samples from AD patients (Jin et al. 2019, Yi et al. 2016). Treatment of 5xFAD AD mice with the K_{Ca}3.1 inhibitor Senicapoc reduced neuroinflammation and increased neuroplasticity (Jin et al. 2019). Also, in other organs involved in aging, K_{Ca}3.1 channels play an essential role. For instance, a recent study showed protective effects of K_{Ca}3.1 channels in cardiovascular function in aged mice by reversing endothelial dysfunction without effects on the immune system (Mathew John et al. 2019).

These studies highlight IK_{Ca} channels blockage as a potential treatment for AD.

4.3. SK channels (K_{Ca}2.1/K_{Ca}2.2/K_{Ca}2.3)

4.3.1. Alzheimer's Disease and aging

The delicate balance involving SK channels' function in the CNS reflects their critical function in AD. Cortical samples from AD patients display higher expression of a shorter variant of SK2 (Murthy et al. 2008). Screening of alternative splice variants by microarray assays in AD human brain and their bioinformatic analysis revealed significant changes in splicing patterns of *KCNN1* and *KCNN2* genes, suggesting that their function might be compromised during AD pathology (Heinzen et al. 2007). *In vivo* studies in mice with lesioned hippocampus showed that treatment with apamin displayed an enhanced performance in water maze tests (Ikonen and Riekkinen 1999, Messier et al. 1991).

Interestingly, the fact that SK_{Ca} channels have been found to be alternatively spliced in AD could possibly be linked to the dysregulation in intracellular Ca²⁺ commonly associated with AD (Heinzen et al. 2007). Moreover, LTP leads to the internalization of these channels mediated by PKA phosphorylation, promoting neuroplasticity (Lin et al. 2008). Agreeing with these results, SK3 expression in aged hippocampal neurons contributes to reduced LTP and impaired trace fear conditioning (Blank et al. 2003). On a mechanistic level, the importance to hippocampal neurons is evidenced by the inhibition of SK_{Ca} channels with apamin, which leads to augmented excitability of hippocampal neurons, LTP, and synaptic plasticity, which translated into an enhanced cognitive performance (Stackman et al. 2002, Ngo-Anh et al. 2005). Similarly, in TgCRND8 AD mice, inhibition of SK_{Ca} channels improved cholinergic function and nicotinic excitation, suggesting a novel target for the treatment of attention deficits in AD (Proulx et al. 2015, Proulx et al. 2019). Additionally, K_{Ca}2.3/SK3 channel overexpression induced LTP deficiency in hippocampal slices. In addition, changes were found at the mRNA levels of genes involved in neurodegeneration such as the upregulation of dopamine receptors, GABA receptor, and APP increase (Martin et al. 2017). However, SK3 depletion in the cerebellum was sufficient to induce ataxia in transgenic mice by disrupting afterhyperpolarization and thus increasing spontaneous firing (Shakkottai et al. 2004).

Regarding SK_{Ca} channels in other cell types next to neurons in AD, it has been found that even if they are present in platelets, they were unresponsive to their inhibition (de Silva et al., 1998). SK_{Ca} channels play also a role in aging-related endothelial dysfunction, which is in part manifested as an impairment of NO-mediated relaxation, but interestingly a reduced function of SK_{Ca} channels was also found (Kong et al., 2015a). A recent study addressed the question of how endothelial function is altered during aging and whether there is a difference between female and male cerebral arteries response to SK_{Ca} channel modulation. It was demonstrated that the sensitivity of SK_{Ca}/IK_{Ca} channel activation mildly decreases in females compared to males during aging (Hakim et al. 2019). The authors have suggested that these changes together with the altered function of GPCRs might contribute to maintaining optimal cerebral blood flow in females versus males during old age.

4.3.2. Neuroinflammation

An increasing number of studies report the implication of SK_{Ca} channels on ROS production. In AD, one key characteristic is the activation of microglia, that contribute to the disease progression by releasing reactive oxygen intermediates, a process primed by Aβ oligomers (Van Muiswinkel et al., 1996). Interestingly, blocking SK_{Ca} channels present in microglia and astrocytes was found to inhibit this respiratory burst (Khanna et al. 2001). Moreover, activation of SK_{Ca} channels significantly reduced LPS-stimulated microglia activation via attenuation of intracellular Ca²⁺ levels and reduced downstream events including TNF-α and IL-6 cytokine production and nitric oxide (NO) release in activated microglia (Dolga et al. 2012) (Fig. 1C).

4.3.3. Mitochondrial function and Ca²⁺ signaling

As discussed in the previous section, it appears that blockers of SK_{Ca} channels can alleviate memory deficits, while SK_{Ca} channel activators worsen memory. However, in many cases, SK_{Ca} channel activation promotes neuroprotection. Upon glutamate cytotoxicity in cerebral ischemia and rotenone challenge in dopaminergic neurons, positive modulation of the channel resulted in decreased intracellular Ca²⁺, and modulation of NADPH oxidase, reduction of ROS production and consequently leading to preservation of mitochondrial transmembrane potential, mitochondrial dynamics and diminished apoptosis (Allen et al. 2011, Dolga et al. 2014) (Fig. 1B). In addition, in cells lacking NMDAR, it was found that SK_{Ca} channels still exert protective effects via their localization on the IMM. The protection against glutamate-induced oxytosis was mediated via mechanisms involving attenuation of mitochondrial Ca²⁺ (Dolga et al. 2013, Honrath et al., 2017a, 2017b) (Fig. 1D). Thus, it is thought that SK_{Ca} channels located at the IMM are equally important for the modulation of Ca²⁺ intracellular signaling and neuronal viability. Interestingly, this protective phenotype is observed even in conditions in which mitochondria-ER membrane contact points are strengthened by genetically encoded bifunctional linkers, where mitochondrial Ca²⁺ influx and vulnerability to oxidative stress are increased (Honrath et al. 2018).

In addition to mitochondrial Ca²⁺ overload, alterations of ER Ca²⁺ homeostasis can lead to detrimental accumulation of the cytosolic Ca²⁺ that results in progressive neuronal cell death in neurodegenerative disorders. Under conditions of prolonged (long-term) or severe (short-term) ER stress, unfolded protein response (UPR) is initiated and this was detected in post-mortem human AD brains (Matus et al., 2011). Interestingly, the activity of ryanodine receptor (RyR) is increased in 3xTg-AD mice activity. As a consequence, the increase in RyR-mediated Ca²⁺ release from the ER stores seems to be paralleled and compensated by an increase in the activity of postsynaptic SK_{Ca} channels (Chakroborty et al. 2015). Dysfunctional presynaptic and postsynaptic calcium signaling conceal the underlying synaptic depression in pre-symptomatic AD mice. Moreover, it was shown that SK2 channels are present in ER membranes of neuronal HT22 cells, and their activation by CyPPA protected against cell damage initiated by the ER stressors (Richter et al. 2016). Sustained cytosolic Ca²⁺ levels and low ER Ca²⁺ load during ER stress could be largely restored by the activation of SK2 channels (Richter et al. 2016).

In our previous studies, we observed that SK_{Ca} channel activation alone induced a mild increase in mitochondrial ROS levels (Richter et al. 2015). Recently we found that this process is implicated in the protection against oxidative toxicity in neurons, since scavenging mitochondrial ROS diminished the SK_{Ca}-mediated protection (Krabbendam et al. In Press). These data suggest a beneficial role for mitohormesis providing an adaptive phenotype for later situations of oxidative stress (Fig. 1D). The implication of SK_{Ca} channels in this mechanism suggests that these channels might represent a potential target for neurodegenerative diseases, since processes underlying the pathophysiology of AD, Parkinson's disease and aging include mitochondrial oxidative stress (Carvalho et al. 2015, Onyango 2018). Furthermore, due to the fact that neurons are extremely dependent on

oxidative phosphorylation to obtain the high amount of energy required for its normal functioning (Herrero-Mendez et al. 2009), mitochondrial dysfunction can be detrimental. Interestingly, concomitantly with the induction of slight mitochondrial ROS production following SK_{Ca} channel activation, mitochondrial complex activity was decreased, and an initial increase in glycolysis was observed in neuronal cells that provided protection against oxidative stress (Krabbendam et al. In Press). Notably, in the brain cortex of AD patients elevated levels of the glycolytic enzymes pyruvate kinase and lactate dehydrogenase A (LDHA) were found (Bigl et al. 1999). Furthermore, increased levels of pyruvate dehydrogenase kinase, and concomitantly increased activity of LDHA led to enhanced aerobic glycolysis which protected against Aβ toxicity in various neuronal lines (Newington et al., 2013, Newington et al. 2011). Deficiencies in glycolysis are also age-related (Dong and Brewer 2019). In longevity studies in *C. elegans*, we have observed that activation of SK_{Ca} channels increases the median life-span. In addition, SK channel activation increased the worm resistance to heat-induced stress and improved survival (Krabbendam et al. In Press).

These results may reflect that the subcellular localization and alternative splicing balance of these channels are worth investigating to better understand their role during aging and the pathology of neurodegenerative diseases linked to both memory formation and cell survival.

5. Perspectives in intervention strategies

K_{Ca} channels modulate subcellular [Ca²⁺], resulting in the modulation of action potential propagation and cellular viability. K_{Ca} function is deeply associated with its subcellular localization and can lead to synaptic dysfunction. In this regard, the use of K_{Ca} activators has been proposed as neuroprotective in cardiac/brain ischemia models, while K_{Ca} blockers have been proposed for the treatment of different neurodegenerative conditions, such as Parkinson's disease, multiple sclerosis, and AD. However, both BK_{Ca} and SK_{Ca} channel activity was also shown to be crucial for the cerebellar neuron spiking frequencies. Therefore, inhibition of these channel activity is likely to cause ataxia. BK_{Ca} channel activity was also shown to be important for functional hyperemia. Thus, its pharmacological suppression might induce dysfunctional neurovascular coupling, favoring AD progression. Nonetheless, in the last decade, K_{Ca} action role in neuroprotection has been unveiled, especially associated with these channels' localization in the mitochondria, which enables them to tamper ROS production by inhibiting mitochondrial Ca²⁺ overload and preservation of the respiratory chain reaction. Thus, K_{Ca} channels expressed in the mitochondria might be important for neuroprotection.

Several K_{Ca} channel modulators have been characterized (extensively reviewed in (Honrath et al., 2017a)), but their potential use faces the challenge of altering the global activity of these proteins. Further studies on the selective modulation of membrane versus mitochondrial K_{Ca} might be valuable to translate their fine-tune modulation of Ca²⁺ signaling to the clinic.

Declaration of Competing Interest

The authors declare no conflict of interest regarding the publication of this paper.

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